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## Maturation of Gut Microbiota and Circulating Regulatory T Cells and Development of IgE Sensitization in Early Life

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# A Single-Center Comparison of Extended and Restricted THROMBOPROPHYLAXIS with LMWH after Metabolic Surgery

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## Abstract

**Introduction** Morbid obesity is an important risk factor for developing a venous thromboembolic events (VTE) after surgery. Fast-track protocols in metabolic surgery can lower the risk of VTE in the postoperative period by reducing the immobilization period. Administration of thromboprophylaxis can be a burden for patients. This study aims to compare extended to restricted thromboprophylaxis with low molecular weight heparin (LMWH) for patients undergoing metabolic surgery.

**Methods** In this single center retrospective cohort study, data was collected from patients undergoing a primary Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) between 2014 and 2018. Patients operated in 2014–2017 received thromboprophylaxis for two weeks. In 2018, patients only received thromboprophylaxis during hospital admission. Patients already using anticoagulants were analyzed as a separate subgroup. The primary outcome measure was the rate of clinically significant VTEs within three months. Secondary outcome measures were postoperative hemorrhage and reoperations for hemorrhage.

**Results** 3666 Patients underwent a primary RYGB or SG following the fast-track protocol. In total, two patients in the 2014–2017 cohort were diagnosed with VTE versus zero patients in the 2018 cohort. In the historic group, 34/2599 (1.3%) hemorrhages occurred and in the recent cohort 8/720 (1.1%). Postoperative hemorrhage rates did not differ between the two cohorts (multivariable analysis,  $p = 0.475$ ). In the subgroup of patients using anticoagulants, 21/347 (6.1%) patients developed a postoperative hemorrhage. Anticoagulant use was a significant predictor of postoperative hemorrhage ( $p < 0.001$ ).

**Conclusion** Despite the restricted use of thromboprophylaxis administration since 2018, the rate of VTEs did not increase. This may be explained by quick mobilization and hospital discharge, as encouraged by the fast-track protocol. There was no significant difference in postoperative hemorrhage rates by thromboprophylaxis protocol. Short term use of thromboprophylaxis in metabolic surgery is safe in patients at low risk of VTE.

**Keywords** Roux-en-Y gastric bypass · Sleeve gastrectomy · Hemorrhage · Pulmonary embolism · Deep venous thrombosis · ERABS · Enhanced recovery

## Abbreviations

ASMBS	American Society for Metabolic and Bariatric Surgery
BMI	body mass index
CI	confidence interval
DOAC	direct oral anticoagulant
DVT	deep venous thrombosis
ERABS	enhanced recovery after bariatric surgery
IRB	institutional review board
LMWH	low molecular weight heparin
OR	odds ratio
PE	pulmonary embolism
RYGB	Roux-en-Y gastric bypass
SG	sleeve gastrectomy

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TWOR	toetsingscommissie wetenschappelijk onderzoek Rotterdam
VKA	vitamin K antagonist
VTE	venous thromboembolic events

## Introduction

Severe obesity (body mass index (BMI)  $\geq 40$  kg/m<sup>2</sup>) is associated with increased mortality rates, with most deaths attributed to heart disease, cancer and diabetes [1]. These increased risks can largely be reversed by significant weight loss, which is most permanently achieved by metabolic surgical procedures [2]. Whilst these procedures are safe, morbidly obese patients are at increased risk of developing short-term postoperative complications [3, 4]. Reduction of BMI-related health risks are thought to outweigh the risks of metabolic surgery such as venous thromboembolic events (VTE) with high mortality rates [5].

Rates of deep venous thrombosis (DVT) and pulmonary embolism (PE) after metabolic surgery are moderate: 0.3–2.2% within one month after surgery for DVT and 1% for PE [4]. Nevertheless, PE plays an important role in the mortality of this patient category and guidelines advice to administer prophylactic low molecular weight heparin (LMWH) perioperatively and after discharge to all patients undergoing metabolic surgery [6, 7]. There is no consensus on type, dosage or duration of prophylaxis, but a recent publication from the American Society for Metabolic and Bariatric Surgery (ASMBS) Clinical Issues Committee suggested that extended pharmacological thromboprophylaxis can be restricted to only those patients who are deemed high risk of developing venous thromboembolic events (VTEs) [6]. Guidelines for perioperative care in metabolic surgery with respect to the Enhanced Recovery After Bariatric Surgery (ERABS) protocols recommend early mobilization and mechanical prophylaxis, such as intermittent pneumatic compression or graduated compression stockings. However, there are also guidelines that additionally encourage extended use of thromboprophylaxis for three to four weeks [7]. The effect of exclusive preoperative and/or extended pharmacological thromboprophylaxis on the incidence of postoperative bleeding is currently unknown.

Over the years, multiple studies have been published on the advantages of following an ERABS protocol. One of the most important items in these fast-track protocols is to stimulate early mobilization after surgery, thereby allowing for early hospital discharge and reducing the number of VTEs. At the same time, the fast-track program aims to prevent overtreatment with potentially unnecessary pharmacological thromboprophylaxis. Studies suggest that the rate of VTE after laparoscopic metabolic surgery nowadays is relatively low [8, 9], while the incidence of major bleeding seems to increase

[10, 11]. Thus, not only preventive measures for VTE should be undertaken, but also for postoperative hemorrhage.

This study aims to investigate if the VTE risk of restricted LMWH prophylaxis is sufficiently low in patients undergoing metabolic surgery with no or little risk factors besides their obesity. In addition, we assessed whether the risk of postoperative hemorrhage decreased when the duration of thromboprophylaxis was shortened.

## Methods

### Design and Data Collection

We performed a retrospective cohort study using two cohorts (details mentioned below). Data was collected prospectively from all patients undergoing a primary Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) between January 2014 and December 2018 in a single center teaching hospital. The mean ( $\pm$  SD) duration of surgery was  $53 \pm 19$  min for RYGB and  $36 \pm 13$  min for SG. The median (IQR) length of hospital stay for the complete cohort was 1.17 (0.18) days. The primary outcome measure was the clinically significant VTE within three months postoperatively. Secondary outcome measures were postoperative hemorrhage within one month and reoperation for postoperative hemorrhage within one month.

### Cohorts

All patients were treated in accordance with the ERABS protocol in use in that period [12]. Two cohorts were formed according to the two regimens of thromboprophylaxis; I) 2014–2017: Extended thromboprophylaxis: Dalteparin 5000 IE from 12 h pre-operatively until two weeks postoperatively for all patients; II) 2018: Restricted thromboprophylaxis: Dalteparin 5000 IE only during hospital admission, starting postoperatively. High risk patients were identified according to the Caprini score (Table 1) [13] and received pharmacological thromboprophylaxis according to the 2014–2017 protocol: Dalteparin 5000 IE starting the day before surgery and continuing until two weeks postoperatively. Patients who had had previous VTEs were advised to wear their own stockings. Patients using vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) would bridge the perioperative period using a prophylactic dosage of Dalteparin instead of therapeutic, because of the non-negligible risk of postoperative hemorrhage.

The protocol alteration to restricted thromboprophylaxis in 2018 was implemented because the risk of hemorrhage was thought to exceed the risk of VTE and based on gained experience with pharmacological thromboprophylaxis, and supported by the work of Blanchet et al., showing that extended

**Table 1** Caprini score and treatment per patient group

Patient group	Treatment
Therapeutic anticoagulants	Pre- and postoperative bridging with Dalteparin 1 dd 5000 IE, continue until INR is adequate
• Vitamin K antagonists	
• Direct Oral Anticoagulant (DOAC)	Dalteparin 5000 IE from 1 day pre-operatively until 14 days postoperatively
• Low Molecular Weight Heparin (LMWH)	
One or more risk factors:	In case of medical history of VTE: Patient wears own stockings
• Age $\geq 75$ years	
• Medical history of VTE	Dalteparin 1 dd 5000 IE during hospital admission
• Known hereditary thrombophilia*	
• Recent cerebrovascular accident ( $\leq 1$ month)	
• Malignancy	
No risk factors	

\*For example protein C-, protein S-, or antithrombin-deficiencies, factor V Leiden, prothrombin 20210A mutation

pharmacological prophylaxis can increase the incidence of postoperative bleeding [11].

## Types of Surgery

The surgical techniques did not change over the years for any of the procedures [14–16]. For SG, clips are applied on the staple line in case of visible bleeding in normotensive patients. In some cases of peroperative bleeding, a drain is placed, which is removed the next day in case of no or little production. The RYGB is checked at the entero-enterostomy and gastro-enterostomy for bleeding spots. During the operation and certainly towards the end, the aim is to keep the patient normotensive and to control the possible bleeding spots properly.

## Postoperative Complications

VTE was defined as clinically apparent VTE, as no routine venous duplex ultrasound of the calf veins was performed. On the first postoperative day, patients were asked about complaints of calf pain as part of the ERABS protocol postoperative checklist [17]. In case of a positive answer, physical examination would be performed, followed by diagnostic imaging of the calf veins, if indicated, by venous duplex ultrasound. This treatment pathway also applies to patients presenting themselves at the emergency ward or outpatient clinic with complaints of calf pain.

Postoperative hemorrhage was confirmed when clinically apparent (e.g., hematemesis or melena) or when visualized on diagnostic imaging or during reoperation. In several cases, hemorrhage was suspected based on clinical and chemical parameters such as tachycardia, hypotension, severe abdominal pain in combination with a decrease in hemoglobin. In these patients, no diagnostic imaging was performed and tranexamic acid was administered pragmatically, 1000 mg

per dose, and repeated after a minimum of six hours if considered necessary by the surgeon. If a hemorrhage was not confirmed by diagnostic imaging and the patient was hemodynamically stable, cases were classified as ‘no hemorrhage’.

## Statistical Analysis

All analyses were performed using SPSS (PASW) 25 software (SPSS Inc., Chicago, Illinois, USA). The risk of VTE in the two cohorts with different thromboprophylaxis regimens was compared using the binomial test, testing the hypothesis that not more than three VTE cases occur when restricted thromboprophylaxis regimen II is implemented. For patients without anticoagulants use, risks of hemorrhage in the two regimens were compared using Fisher’s Exact test. Moreover, the adjusted risk of hemorrhage was analyzed with multivariable binary logistic regression analysis, with presence of hemorrhage as the dependent variable and the two thromboprophylaxis regimens (one dummy variable) as independent variables, adjusting for patient characteristics, type of surgery and presence of comorbidities. All characteristics listed in Table 2 were also included to avoid that differences between regimens I and II could be attributed to differences in casemix between regimens. A similar multivariable logistic regression analysis was performed to assess the difference in risk of postoperative hemorrhage between patients with and without anticoagulant use. Results were evaluated at a significance threshold of  $p < 0.05$  (two-sided).

## Results

Between 2014 and 2018, 3666 patients underwent a primary RYGB ( $n = 1983$ ) or SG ( $n = 1683$ ). Over the years, popularity of the sleeve gastrectomy as opposed to the RYGB gradually increased from 296/669 (44.2%) in 2014 to 437/777

**Table 2** Baseline characteristics based on thromboprophylaxis regimen

	No anticoagulants use; 2 weeks thromboprophylaxis (regimen I, <i>n</i> = 2599)	No anticoagulants use; thromboprophylaxis during hospitalization (regimen II, <i>n</i> = 720)	<i>p</i> value
Female, <i>n</i> (%)	2145 (82.5%)	592 (82.2%)	0.847
Age (years), mean $\pm$ <i>sd</i>	40.5 $\pm$ 11.0	40.1 $\pm$ 11.4	0.759
Baseline BMI (kg/m <sup>2</sup> ), mean $\pm$ <i>sd</i>	43.4 $\pm$ 4.8	42.8 $\pm$ 4.9	0.001
RYGB, <i>n</i> (%)	1460 (56.2%)	309 (42.9%)	<0.001
Presence of hypertension, <i>n</i> (%)	655 (25.2%)	166 (24.1%)	0.552
Presence of T2D, <i>n</i> (%)	404 (15.6%)	74 (10.8%)	0.001
Presence of dyslipidemia, <i>n</i> (%)	300 (11.6%)	41 (6.0%)	<0.001

(56.2%) in 2018. Table 2 shows the baseline characteristics and comorbidities for the two thromboprophylaxis regimens. Significant differences were found between the two regimens for baseline BMI, type of surgery, type 2 diabetes (T2D) and hypercholesterolemia. Table 3 shows the baseline characteristics divided by anticoagulant usage. Patients who used anticoagulants were more often males of older age, and had higher rates of hypertension, diabetes and dyslipidemia compared to patients without anticoagulant use.

Two patients were diagnosed with postoperative VTE in regimen I (2014–17): 2/2599 (0.01%, exact 95%CI: 0.0–0.3%). In regimen II (2018) the postoperative VTE rate was 0/720 (0%, exact 95%CI: 0.0%–0.51%), hereby not exceeding the pre-set threshold of three VTE cases (exact binomial test,  $p > 0.99$ ). Both patients diagnosed with VTE had developed early postoperative complications prior to the VTE occurrence, and did therefore not follow the fast-track protocol.

The absolute hemorrhage rates for patients without anticoagulants use were 34/2599 (1.3%, exact 95%CI 0.9–1.8%) for regimen I (2014–17) and 8/720 (1.1%, exact 95%CI 0.5–2.2%) for regimen II (cohort 2018) ( $p = 0.675$ ). The thromboprophylaxis regimen in the group not on anticoagulant therapy was not significantly associated with higher postoperative hemorrhage rates, adjusted for patient characteristics, type of surgery and comorbidities: OR 1.370, 95%CI 0.577–3.254,  $p = 0.475$ .

The absolute hemorrhage rate for the group with preexisting anticoagulant use was 6.1% (95%CI: 3.9–8.9%) versus 1.3% (95%CI: 0.9–1.7%) without anticoagulant use (Fig. 1). Anticoagulant use was significantly associated with postoperative hemorrhage: OR 3.143, 95%CI 1.642–6.019,  $p = 0.001$ , adjusted for patient characteristics, type of surgery and comorbidities.

In the period of 2014–2016, before the introduction of tranexamic acid, 33/2114 patients (1.6%, exact 95%CI 1.1–2.2%) had a postoperative hemorrhage requiring a reintervention. Of the 1552 patients that underwent a metabolic procedure in 2017–2018 (after implementation of tranexamic acid), 24 (1.5%) patients received tranexamic acid and still underwent a reintervention due to hemorrhage. Six additional (0.4%) patients underwent a reintervention, but did not receive tranexamic prior to this. Another 35 (2.3%) patients received tranexamic acid and did not undergo a reintervention.

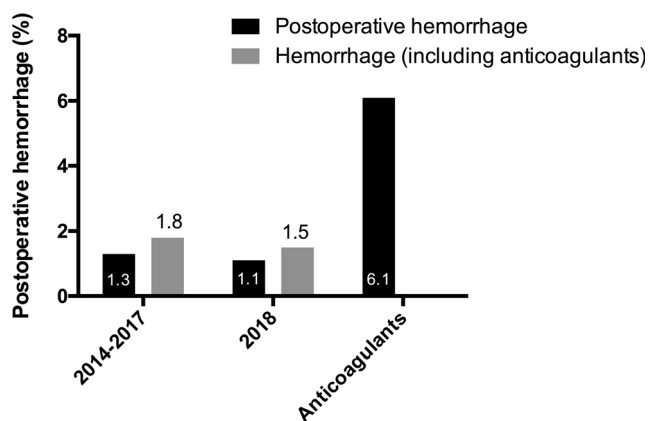
## Discussion

This study aimed to determine the safety of a restricted policy of pharmacological prophylaxis for VTE in patients undergoing metabolic surgery with no or few risk factors besides their obesity, and to determine the risk of postoperative bleeding

**Table 3** Baseline characteristics based on anticoagulants use

	Anticoagulants use ( <i>n</i> = 347)	No anticoagulants use ( <i>n</i> = 3319)	<i>p</i> value
Female, <i>n</i> (%)	231 (66.6%)	2737 (82.5%)	<0.001
Age (years), mean $\pm$ <i>sd</i>	50.6 $\pm$ 8.9	40.5 $\pm$ 11.0	<0.001
Baseline BMI (kg/m <sup>2</sup> ), mean $\pm$ <i>sd</i>	42.2 $\pm$ 5.2	43.3 $\pm$ 4.8	<0.001
RYGB, <i>n</i> (%)	214 (61.7%)	1769 (53.3%)	<0.001
Presence of hypertension, <i>n</i> (%)	196 (57.3%)	821 (24.7%)	<0.001
Presence of T2D, <i>n</i> (%)	110 (32.2%)	478 (14.4%)	<0.001
Presence of dyslipidemia, <i>n</i> (%)	143 (41.8%)	341 (10.3%)	<0.001





**Fig. 1** Crude postoperative hemorrhage rates per thromboprophylaxis regimen. There were no significant differences in hemorrhage rates by thromboprophylaxis regimen either including ( $p = 0.674$ , gray bars) or excluding ( $p = 0.675$ , black bars) patients with anticoagulant use

under different pharmacological thromboprophylaxis protocols. This study showed that a VTE was observed in none of the patients managed according to the restricted thromboprophylaxis protocol. A total of two of the patients with an intention-to-treat according to the fast-track protocol developed a VTE, both with extended use of thromboprophylaxis. Adequate thromboprophylaxis is considered to be of great importance because of the high mortality rate associated with VTE [8]. Therefore, the ERABS guidelines recommend both pharmacological prophylaxis and compression devices of the lower extremities [7]. Quick mobilization after surgery might be an even more important aspect in preventing VTE. In the fast-track setting, mobilization starts directly after surgery. On the first postoperative day, physical therapists practice mobilization and advise patients on how to mobilize after discharge.

Before the introduction of fast-track programs, VTE was a feared complication of metabolic surgery and a significant contributor of the mortality associated with these procedures [18]. In 2007, Raftopoulos et al. concluded that extended thromboprophylaxis was safe and effective in reducing the incidence of VTE as compared to in-hospital thromboprophylaxis only [19]. The authors mention a mean duration of surgery of 220 min. The current study showed a mean duration of surgery of 53 min for RYGB and 36 min for SG in our cohort, supporting the earlier findings that duration of surgery independently influences the risk of VTE [20].

Nowadays, the incidence of VTE after laparoscopic metabolic surgery is relatively low [8] which is also confirmed in our study: only two patient developed VTEs. Interestingly, these patients did not follow the fast-track protocol because of short-term postoperative complications. In one case, the patient was readmitted within one week postoperatively and underwent a reoperation because of staple line leakage. During a two month hospital admission because of persistent staple line leakage and the patient being bedridden and in a

poor clinical condition, the patient eventually developed a DVT while on thromboprophylaxis. In the second case, the pharmacological thromboprophylaxis was paused directly after surgery, because of suspicion of postoperative hemorrhage that was later confirmed on diagnostic imaging. After several days of bedrest due to poor clinical condition and no safe possibility to administer thromboprophylaxis, pulmonary embolisms occurred. These two cases emphasize the importance of close monitoring for the presence of VTE in patients that do not follow the fast-track protocol.

The importance of close monitoring of patients with an extended length of hospital stay was also shown by Froehling et al. The authors state that the incidence of VTE rose from 0.3% to 1.9% between thromboprophylaxis for seven and 30 days postoperatively [21]. However, the patients that developed VTEs had a mean length of hospital stay of six days. In the current study, the median length of hospital stay was 1.16 days.

Our results, supported by the available literature, demonstrate that a short length of hospital stay (during which mobilization is encouraged) can be beneficial for patients. However, the window to detect complications during admission is small. It is suggested that the incidence of major bleeding is increasing [10]. More specifically, postoperative hemorrhage occurs in 2.0% of patients undergoing SG and in 1.5–3.1% of patients undergoing a RYGB [22, 23]. While our results are in line with these rates (2.2% for SG and 1.3% for RYGB), our study does not corroborate the increasing trend.

As expected, the rates of postoperative hemorrhage were higher in patients using anticoagulants. Also, this patient group had higher rates of hypertension, diabetes and dyslipidemia, suggesting that these patients' clinical condition was already worse preoperatively. The study by Coblijn et al. found that the use of anticoagulants is associated with postoperative complications (OR 1.5, 95%CI 0.884–2.394,  $p = 0.142$ ) [24]. Our results correspond to these findings.

Postoperative hemorrhage can have a very serious course and prevention of hemorrhage should therefore receive at least equal attention as prevention of VTE. In 2017–2018, patients that were suspected of postoperative hemorrhage were given tranexamic acid, a plasminogen inhibitor that can reduce blood loss by inhibiting fibrinolysis [25]. This decision was mainly influenced by the patient's clinical condition, the direct availability of an operating room and the surgeon-on-call's experience with tranexamic acid. Klaassen et al. performed a retrospective analysis on postoperative administration of tranexamic acid in case of suspected hemorrhage and suggested that tranexamic acid can reduce the reoperation rate for bleeding after metabolic surgery [26]. Our retrospective study has insufficient power to draw a conclusion on the possible prevention of reoperations due to administration of tranexamic acid. Because of the increasing experience with

tranexamic acid over the years and the negligible disadvantages, the threshold to prescribe tranexamic acid in case of suspicion of hemorrhage is currently low. A randomized controlled trial should further investigate the effects of tranexamic acid administration on the reoperations rates for hemorrhage.

Many studies report on either the risk of VTE or the risk of postoperative hemorrhage. No articles were found on the optimal balance between VTE risk and hemorrhage risk in patients undergoing metabolic surgery and following a fast-track program. Altieri et al. do report on both the risk of VTE and the risk of hemorrhage and conclude that postoperative VTE chemoprophylaxis is associated with decreased VTE events compared to no prophylaxis, while minimizing hemorrhage compared to pre-operative prophylaxis [27]. However, their patients did not follow a fast-track protocol, which is known to accelerate mobilization and shorten hospital stay. To our knowledge, this article is the first to demonstrate that a restricted thromboprophylaxis strategy for certain low-risk patients while following the fast-track protocol does not increase the risk of VTE.

This study has several limitations. It was a single-center, retrospective study and cohorts were consecutive instead of parallel in time. However, these factors did not contribute to heterogeneity of the cohorts, except for the type of surgery. The sample size of regimen II was limited, VTE is a rare event and observed VTE incidence rates were low. A formal comparison of regimens I and II in a randomized controlled trial would require at least 98,000 patients per treatment arm to demonstrate the superiority of regimen II, and a non-inferiority study probably would require even more patients. Such an unrealistically large study would clearly be unfeasible. As such, our study does not demonstrate in absolute terms that regimen II is superior (or non-inferior) to regimen I. However, what our study actually does show is that it is highly likely that the observed VTE rate of regimen II is below a reasonably chosen threshold of three VTE cases. Also, routine venous duplex ultrasound was not performed. Therefore, only clinically significant VTEs could be registered, and there may have been some underreporting. However, it is unclear whether the not-clinically apparent VTEs are relevant to diagnose and should receive aggressive therapy when diagnosed. Unfortunately, due to the retrospective aspect of this study, it was not possible to perform a valid comparative analysis on the effects of tranexamic acid on postoperative hemorrhage. Therefore, the results were stated purely in descriptive terms and we refrained from any conclusions regarding tranexamic acid use. We aim to address this matter in future research projects.

## Conclusion

This study demonstrates that a restricted thromboprophylaxis strategy did not adversely affect the rates of VTE and postoperative hemorrhage for patients following the fast-track

protocol with no preexisting risk factors for VTE. Furthermore, our study underlines that patients using anticoagulants have an increased risk of postoperative hemorrhage as compared to patients not on anticoagulant therapy. From our data, we cannot conclude if administration of tranexamic acid for clinical suspicion of hemorrhage could prevent reintervention after metabolic surgery. Large national databases could play an important role in further research on the topic of short term thromboprophylaxis. Also, future studies should focus on prevention of postoperative hemorrhage in patients with a restricted thromboprophylaxis strategy following the fast-track protocol.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the institutional review board (IRB) and the regional Medical Research Ethics Committee TWOR, Rotterdam, the Netherlands (protocol number 2018–03).

**Informed Consent** Informed consent was obtained from all individual participants included in the study.

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